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December 22, 1997

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Document Control Officer
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

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Attention: 8(e) Coordinator

Dear Sir: **COMPANY SANITIZED**

Re: Normal Propyl Bromide (CAS# 106-94-5)

This letter is submitted in accordance with Section 8(e) of the Toxic Substances Control Act, 15 USC 2607(e), and the Environmental Protection Agency's "Statement of Interpretation and Enforcement Policy", 43 FR 1110, 35 seq., March 16, 1978.

It has come to our attentiion that a paper on 2-bromopropane and 1-bromopropane was presented at the 1997 Tokai Region Conference in Japan. The Conference was held in November and was sponsored by the Japan Industrial Hygiene Institute. We have enclosed the Japanese handout of the presentation and an unofficial English translation.

The paper reports Wistar rats were exposed to 1-bromopropane or 2-bromopropane. Wistar rats exposed to 1000 ppm of 1-bromopropane exhibited paralysis of hind legs among other effects after 5-7 weeks of daily 8-hour exposures. They were sacrificed at end of 5-7 weeks.

We have done a 90-day inhalation study on 1-bromopropane at 600 ppm and we observed no paralysis of hind legs.

We do not know whether this Japanese study has been published or has been submitted for publication. We are trying to obtain additional information. Should we obtain additional information, we will forward it to the Agency.

If you have any questions, please contact me at [ ]

Sincerely,

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Attachments

Presented at the Japan Industrial Hygiene Institute 1997 Tokai Region Conference
Aichi Medical College
November 7, 1997

Neurotoxicity of 1-BP & 2-BP

by unidentified, Ichihara, Shah, Kitoh, Shibata, Takeuchi (Nagoya Univ.) And
Tomoeda(Sanwa Chemical Safety Research Inst.)

(Purpose) In Korea in 1995, it was reported that the workers of an electronic parts production factory had depression of reproductive and blood forming functions. 2-BP (CFC substitute) was the major suspect. We have already uncovered the fact based on our animal experiment that 2-BP has specific toxicity on a spermary, the ovaria, and medullae.

It is said that the Korean workers who exposed to 2-BP also had problems with the peripheral nervous system such as numbness of hands, etc. We conducted the 12wks inhalation test using rats to reveal the followings:

1) Nerve toxicity of 2-BP compared with 1-BP isomer.

2) Toxicity on reproductive and medullary functions at relatively low dosage of 2-BP: 100 ppm.

(Method) Divide 36 Wister male rats into 4 groups (9 each) at random. Using small animal organic solvent exposure chamber, 3 groups were exposed to 2-BP 100 ppm, 2-BP 1,000 ppm and 1-BP 1,000 ppm each for 8 hours/day every day. The reference group was given fresh air only in the chamber. The rats of 1-BP exposure group grew weakest in 5 - 7 wks. All the rats of this group was sacrificed during this period. The rats of 3 other groups were exposed to 2-BP and fresh air for 12 wks. We examined MCV and DL every 4 wks. After 12 wks., all the rats were examined. (detailed fixture methodologies are omitted)

(Results) At 2 wks after the beginning of exposure, the weight increase was markedly suppressed in 1-BP and 1000 ppm 2-BP groups. After 4 wks, 1-BP group rats had statistically significant weight loss compared with 2-BP 1000 ppm group. After 5 - 7 wks, all rats of 1-BP group had paralysis of hind legs. They also had difficulty in walking and the suppression of weight increase. We sacrificed them and performed an autopsy.

In 2-BP 100 ppm group, the weight increase is a little more than that of the reference group. (Fig. 1) In 1-BP 1000 ppm group, MCV decreased significantly in 4 wks. In 2-BP 1000 ppm group, it decreased significantly in 8 wks. The decrease in 12 wks wasn't significant. (Fig.2)

In 4 wks, DL extended in 1-BP 1000 ppm group. DL extended in 2-BP 1000 ppm group in 8 and 12 wks. (Fig. 3) In 1-BP exposure group, the weight decreased in the liver, spleen, spermary, upper part of spermary, prostate gland, seminal vesicle, pituitary gland and brain. In 2-BP 1000 ppm group the weight decreased almost all the organs. In 2-BP 1000 ppm group, the weight decreased significantly in spermary, upper part of spermary, prostate gland and seminal vesicle in the organ/body weight ratio. In 2-BP 1000 ppm group, thrombocyte, erythrocyte and leukocyte counts decreased. In 2-BP 100 ppm group, no significant change was observed. No spermatozoaz was moving in 2-BP 1000 ppm group.

Based on our observation of peripheral nervous system, there was degeneration in axon and myelin in 1-BP 1000 ppm group. In 2-BP 1000 ppm group, the swelling was observed in axon near Ranvier. The same degeneration was observed in 2-BP 100 ppm group but it was less significant compared with that of 2-BP 1000 ppm group. (Fig. 4) In 1-BP 1000 ppm group, the cerebral atrophy degeneration of dorsal cord (Fig. 5) and degeneration of pyramical cells and cerebellar Purkinjee cells were observed. (Fig 6)

(Conclusion)

1) 1-BP has strong toxicity upon central and peripheral nervous systems. 1-BP's reproductive and medullary toxicity is not so significant as that of 2-BP.

2) At 1000 ppm, 2-BP is toxic upon reproduction and medullary functions and peripheral nervous system.

3) It is possible for 2-BP 100 ppm (12 wks exposure) to have influence on peripheral nervous system but it hasn't been definitely shown that it has influence on reproductive and medullary function.

061rls97

平成９年度日本産業衛生学会東海地方会学会事務局
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愛知医科大学衛生学教室
Tel 0561-62-3311 (内線 2312)
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平成９年度

日本産業衛生学会東海地方会学会

プログラム

日　時　平成9年11月7日（金）　9:30～16:40
場　所　愛知医科大学（愛知郡長久手町）
学会長　愛知医科大学衛生学教授　小林　章雄

日本産業衛生学会東海地方会

1－ブロモプロパン及び2-ブロモプロパンの神経毒性

俞 小忠[1]、市原 学[1]、謝 振麟[1]、鬼頭 純三[2]、朝枝 仲幸[3]、
柴田 英治[1]、竹内 康浩[1]
1．名大医衛生 2．名大医動物実験施設 3．三和化学安全性研

[目的] 1995 年、韓国の電子部品製造工場で生殖機能、造血機能低下の症例が報告され、原因物質としてフロン代替品、2-ブロモプロパン（2-BP）が疑われた。我々はすでに動物実験によって 2-BP が精巣、骨髄、卵巣に対する特異的な毒性を有することを明らかにしている。ところで韓国で 2-BP に曝露された労働者の中には、手のしびれなど末梢神経障害を疑わせる症状もみられたと言われている。我々は、1) 2-BP の神経毒性を異性体 1-BP を対照として明らかにするとともに、2) 比較的低濃度 100ppm の 2-BP の生殖、および骨髄毒性を明らかにすることを目的として、ラットを用いた１２週間吸入曝露実験を行った。

[方法] 36 匹ウイスター系雄ラットを９匹ずつ４群に無作為に分け、小動物有機溶剤曝露チャンバーを用いて、曝露群の３群にそれぞれ 2-BP 100 ppm、2-BP 1,000 ppm、1-BP 1,000 ppm を１日８時間、週日曝露した。また、対照群は同チャンバーで新鮮空気のみを与えた。1-BP 曝露群は５週から７週で衰弱が激しくなったため、この期間に同群の全ラットを屠殺した。他の曝露群は 12 週間曝露を続けた。末梢神経毒性の評価のため、尾部の運動神経伝導速度(MCV)、遠位潜時(DL)を４週間毎に測定した。曝露期間終了後、1-BP 群の４匹、および他の曝露群の各１匹をカルノフスキー液で灌流固定し、主要臓器の病理組織標本を作製した。また、その他のラットは屠殺後、血液像および血液生化学的検査、精子数計数、精子形態の観察を行った。精巣はブアン固定し PAS 染色した。脳の染色は Kluver-Barreva の方法で行った。灌流固定したラットの組織は Epon 包埋の後、トルイジンブルーで染色した。統計解析は分散分析の後、群間の比較を Tukey-Kramer の多重比較を用いて行った。

[結果] 曝露２週後、1-BP 群と 1000ppm 2-BP 群の体重増加は著しく抑制された。曝露４週後には 1-BP 群の体重は 1000ppm 2-BP 群に比べ、有意に減少した。曝露５週後から７週後には 1-BP 群の全ラットに後肢麻痺が出現し、歩行障害、体重増加の著しい抑制も認められたので、屠殺して剖検した。2-BP 100 ppm 群では体重は対照群より少し増加した(Fig 1)。1-BP 1000ppm 群では４週でＭＣＶが有意に低下した。2-BP 1000ppm 群では８週で有意な低下を認めた。12 週での変化は有意ではなかった（Fig 2）。曝露４週で 1-BP 1000ppm 群では DL の延長が認められた。８週と 12 週で 2-BP 1000ppm 群では DL の延長が認められた（Fig 3）。1-BP 曝露群では肝臓、脾臓、精巣、精巣上体、前立腺、精嚢、下垂体、脳の重量が減少した。2-BP 1000ppm 群ではほとんど各臓器の重量が減少した。2-BP 1000ppm 群では精巣、精巣上体、前立腺、精嚢の相対重量（体重比臓器重量）が有意に減少した。2-BP 1000ppm では、血小板、赤血球、白血球が減少した。2-BP 100 ppm 群では著明な変化は認められなかった。2-BP 1000ppm では運動精子が見られなかった。解きほぐし法による末梢神経の観察によると、1-BP 1000ppm では axon と myelin に変性が認められた。 2-Bp1000ppm 群では Ranvier の絞輪近傍の axon の Swelling が認められた。2-BP 100ppm 群にも同様の所見が認められたが、2-BP 1000ppm 群ほど著明ではなかった（Fig 4）。1-BP 1000ppm 群では脳の萎縮、後索核の変性（Fig 5）、錐体交差の錐体細胞、小脳プルキンエ細胞の変性が認められた（Fig 6）。

[結論] ①1-BP は中枢神経、末梢神経両方に対して強い毒性を持つ。一方、1-BP の生殖，骨髄毒性は 2-BP ほど著明ではない。②2-BP は 1000ppm で生殖、骨髄毒性の他に主に末梢神経に対して毒性を持つ。③2-BP100ppm 12 週間曝露は末梢神経に対して影響を持つ可能性があるが生殖、骨髄に対する影響は明らかでなかった。

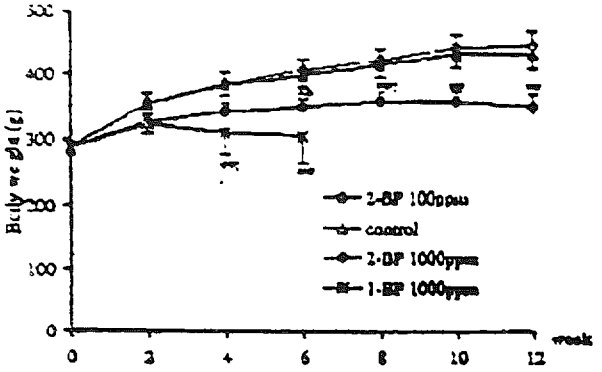

Fig. 1. Time course of body weight (Mean±S.D.). Four rats in the 1-BP group were killed after four weeks' exposure. The remained rats were killed at the end of six weeks' exposure. The rats were killed 16-18 hr after cessation of exposure.

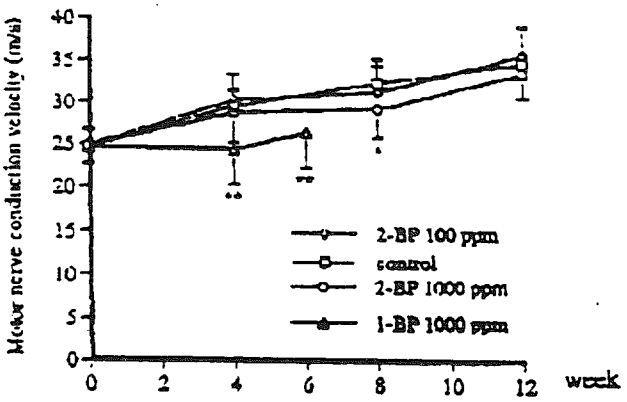

Fig.2 The changes of motor nerve conduction velocity in the rats exposed to 1-bromopropane and 2-bromopropane.(*P<0.05,**P<0.01)

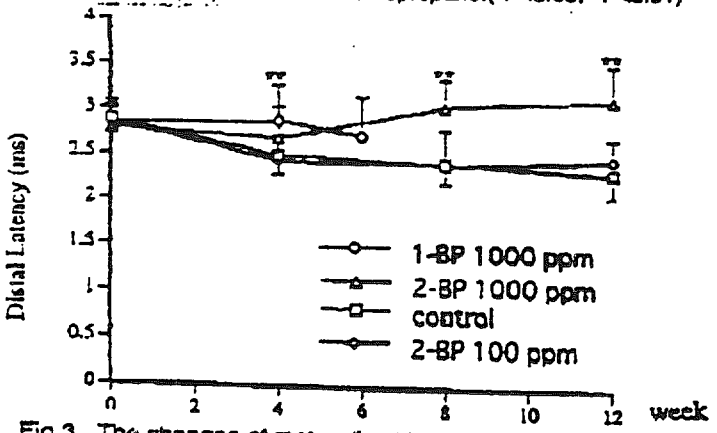

Fig 3. The changes of motor distal latency in the rats exposed to 1-bromopropane and 2-bromopropane. (*P<0.05, **P<0.01)

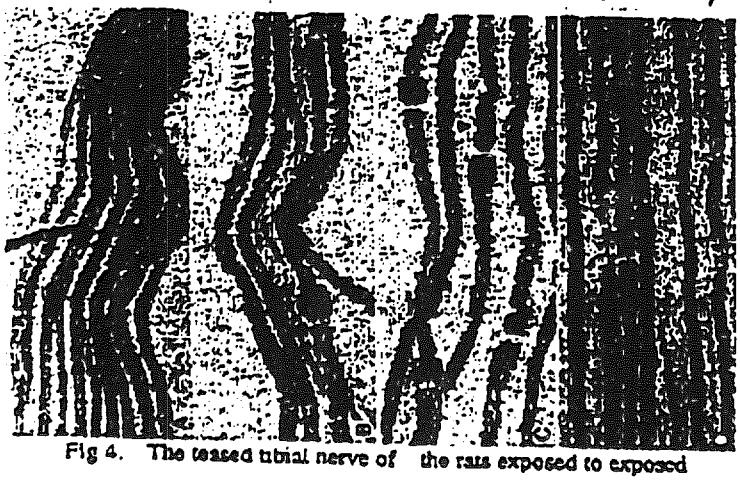

Fig 4. The teased tibial nerve of the rats exposed to exposed to 2-bromopropane at 0 (A), 100 (B), or 1000 ppm (C) for 12 weeks, or rats exposed to 1-bromopropane at 1000

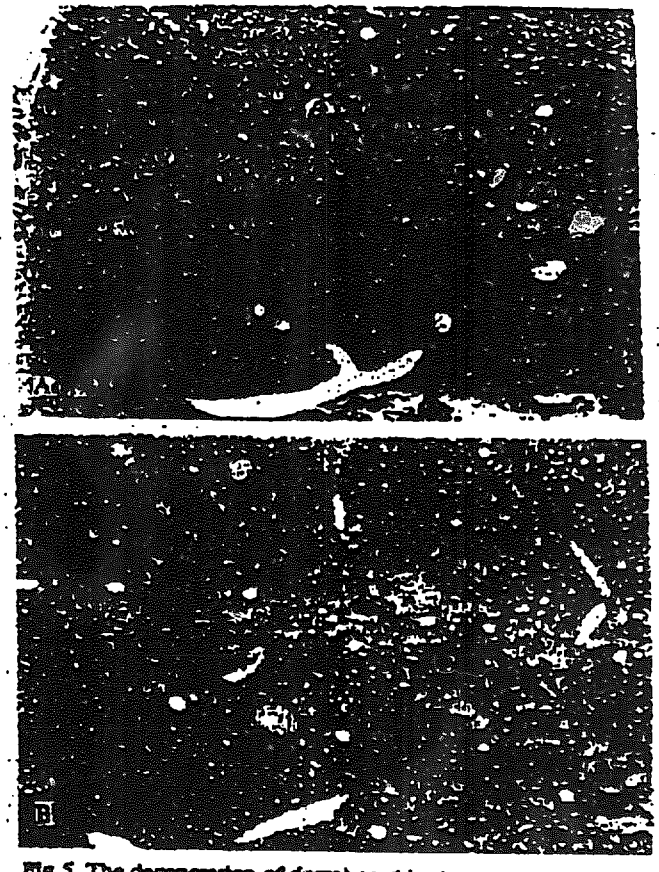

Fig 5. The degeneration of dorsal cord in the rats exposed to 1-bromopropane at 0 ppm (A) or 1000 ppm (B) for 5 or 7 weeks.

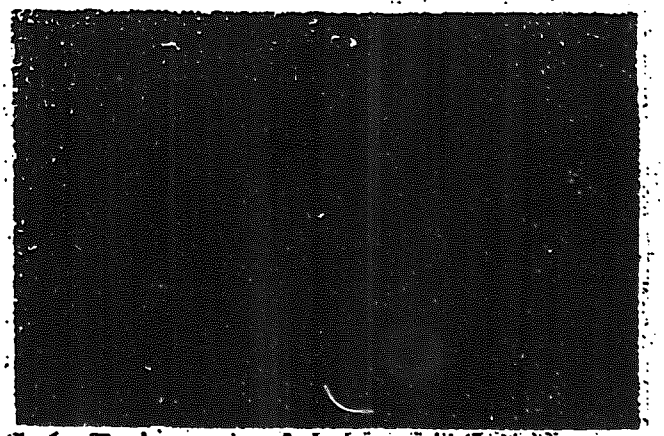

Fig 6. The degeneration of brain pyramidal cells in the rats exposed to 1-bromopropane at 1000 ppm for 5 or 7 weeks.

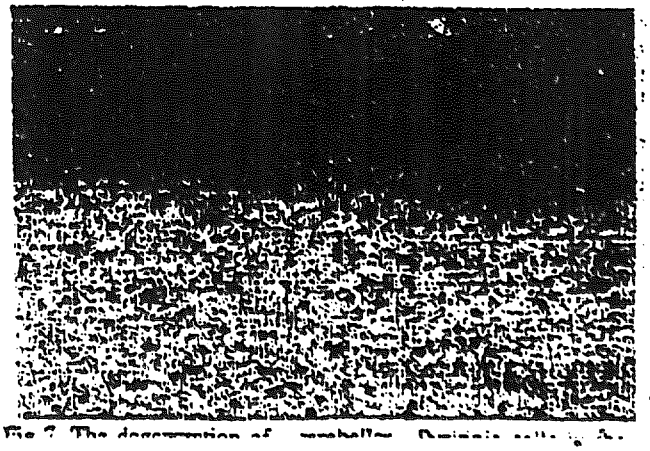

Fig 7. The degeneration of cerebellar Purkinje cells in the